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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/864,873	05/25/2001	John J. Rossi	1954-330	2281
6449	7590	12/19/2003	EXAMINER	
ROTHWELL, FIGG, ERNST & MANBECK, P.C. 1425 K STREET, N.W. SUITE 800 WASHINGTON, DC 20005			LACOURCIERE, KAREN A	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/864,873

Applicant(s)

ROSSI ET AL.

Examiner

Karen A. Lacourciere

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 17 September 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-10 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-10 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

Claims 1 and 3-10 are pending.

#### ***Claim Rejections – 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 3-10 are maintained as rejected under 35 U.S.C. 103(a) as being unpatentable over Michienzi et al. Nucleic acids Symposium Series No. 41, pages 211-214, 1999, cited on PTO form 1449 filed August 2, 2001) in view of Browning et al. (J. Virol. 73(6): 5191-5195, 1999, cited on PTO form 1449 filed August 2, 2001) and Stauber et al. (Virology, 252, p 126-136, 1998, cited on PTO form 1449 filed August 2, 2001), for the reasons of record set forth in the prior Office action, mailed June 17, 2003 and repeated herein.

Michienzi et al. teach a nucleolar delivery system for delivery of a Rev decoy wherein the delivery system comprises a Rev decoy sequence that has replaced an apical loop of U16snoRNA and a C/D box. Michienzi et al. further disclose wherein this decoy is expressed from a vector in a cell under control of a pol III promoter. Michienzi et al. do not teach a Tat decoy comprised in their nucleolar delivery system.

Browning et al. teach a Tat decoy sequence comprising SEQ ID NO:12.

Stauber et al. teach that HIV Tat protein is active in the nucleolus.

It would have been obvious to one of ordinary skill in the art to substitute the Rev decoy sequence in the nucleolar delivery system taught by Michienzi et al. with a Tat decoy sequence, as taught by Browning et al. to provide a vector effective to deliver the Tat decoy to the nucleolus because Rev and Tat were both known to be functional in the nucleolus. One of ordinary skill in the art would have been motivated to substitute the Tat decoy taught by Browning et al. for the Rev decoy taught by Michienzi et al. to make a chimeric RNA for delivery of Tat to the nucleolus because Michienzi et al. teach that this system is effective to deliver a decoy to the nucleolus to investigate the function of the protein which binds to the decoy and Stauber et al. teach that Tat has a role in the nucleolus. One of ordinary skill in the art would have been motivated to make the chimeric Tat decoy claimed in order to further define the role of tat in the nucleolus and to provide a vector to deliver the Tat decoy taught by Browning et al. to a cellular compartment where the target of the Tat decoy is active.

Therefore, the invention of claims 1 and 3-10 would have been obvious as a whole to one of ordinary skill in the art at the time the instant invention was made.

***Response to Arguments***

Applicant's arguments filed September 17, 2003 have been fully considered but they are not persuasive.

In response to the rejection of record of claims 1 and 3-10 under 35 USC 103(a), as being unpatentable over Michienzi et al. in view of Browning et al. and Stauber et al., set forth in the prior Office action (mailed June 17, 2003) Applicant argues that at the time of the invention the skilled artisan would not have been motivated to combine the cited references and Applicant further refers to unexpected results to support the non-obviousness of the invention, but these arguments are not found to be persuasive.

Applicant argues that the skilled artisan would not be motivated to make a chimeric RNA molecule for delivering an HIV TAR RNA (a Tat decoy sequence) to the nucleolus because at the time of the invention Tat was believed to be distributed throughout the nucleus, not just the nucleolus, and therefore there would not be any reason to target TAR to the nucleus. Applicant argues that the primary reference, Michienzi et al. is directed to a decoy for a nucleolar protein, Rev, and the skilled artisan would not combine it with the Tar decoy sequence taught by Browning et al. because the Tat decoy sequence (TAR) used by Browning is not nucleolar targeted.

These arguments have not been found to be persuasive because Both Rev and Tat were recognized in the art as being distributed in multiple compartments in the cell, including the nucleolus. For example, Stauber et al. even refers to these proteins as "the nuclear/nucleolar viral proteins Rev and Tat" and further suggests the benefits of performing similar experiments using Tat and Rev, as their study is directed towards

that aim (see p 126, second column, last paragraph). Although Browning et al. targets their decoy to the nucleus, Browning et al. is not relied upon to teach nucleolar targeting. Browning et al. is relied upon to teach decoy inhibition of Tat and the specifically claimed TAR sequence used in the decoy.

Applicant argues that Stauber et al. does not teach that Tat is active in nucleolus, but instead that the nucleolar localization of Tat is only as a result of overexpression, relying on the statement in Stauber et al. that nucleolar accumulation is “not a prerequisite for function”. Applicant argues that the Stauber et al. reference concludes that Tat shuttles between the nucleus and the cytoplasm and may have a role in the nucleus, but does not suggest that Tat functions in the nucleolus.

These arguments are not persuasive because Applicant is mischaracterizing Stauber et al. and is selectively pointing out statements within Stauber et al. to support their position without considering the teachings of Stauber et al. as a whole. For example, on page 126, second column, last paragraph, Stauber et al. explicitly states that Tat is a nuclear/nucleolar protein. Further, on page 130, 1<sup>st</sup> column, second paragraph, Stauber et al. indicates that natural, untagged Tat is nucleolar by stating “The presence of unlabeled, nuclear/nucleolar Tat in the same cell was verified by a Tat polyclonal antiserum”. Stauber et al. also cites studies wherein Tat was shown to colocalize with nucleolar protein B23 (see for example page 130, second column, last paragraph). Contrary to Applicants assertion that Stauber et al. does not indicate a role for Tat in the nucleolus, Stauber et al. does suggest that Tat has a function in the nucleolus, for example, Stauber et al. states “We reasoned that the nucleolus....may

represent secondary binding sites for Tat when other primary nuclear binding sites are saturated. Demonstrating that Tat is not confined to the nucleus helps to understand how Tat can perform additional functions besides transcriptional activation in the cytoplasm.” (see page 133, first column). Stauber is clearly indicating that Tat has multiple roles, in multiple locations in a cell.

Applicant argues that Stauber et al. teach away from the claimed invention because they teach that the affinity of Tat for the nucleolus was not as strong as Rev and that Stauber et al. suggest that during HIV-1 infection levels of Tat are low suggesting nucleolar accumulation is not important for function. Applicant argues that Stauber et al. would motivate the skilled artisan to inhibit Tat in the cytoplasm, then the nucleus, but not the nucleolus.

These arguments are not persuasive because, read as a whole, Stauber does not teach against a nucleolar function for Tat. The statements Applicant points to in Stauber et al. as teaching against a role for Tat in the nucleolus are actually stating that nucleolar accumulation is not required for Tat function and nucleolar accumulation results from overexpression. As discussed above, Stauber indicates that Tat does occur naturally in the nucleolus (see for example page 130), and further indicates that the nucleolus may provide secondary binding sites for Tat (see for example p 133). These teachings within Stauber et al. would motivate the skilled artisan to make a nucleolar chimeric RNA decoy, as taught by Michienzi et al., comprising the TAR sequence decoy which binds to Tat, as taught by Browning et al., to study the function of Tat in the nucleolus.

Applicant further argues that the unexpectedly high inhibition of Tat and HIV replication using the claimed chimeric RNA molecule, as demonstrated in Figure 12, supports the non-obviousness of the invention. This is not persuasive because Figure 12 is not even present in the specification and there is no data provided to suggest that the claimed chimeric RNA has any unexpected inhibitory properties.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703)



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308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere  
December 15, 2003

~~KAREN A. LACOURCIERE, PH.D.~~  
~~PRIMARY EXAMINER~~

  
KAREN A. LACOURCIERE, PH.D.  
PRIMARY EXAMINER